REMARKS

Status of the Claims

Claims 1-31 were examined.

Claims 1-6, 8-17, 19-25, 27, 28, 30 and 31 are amended.

Claims 3-5, 8-10, 12-14, 19, 20, 21, 23, 27 and 31 are amended only for correcting the linguistic format.

Claims 1, 2, 11, 16 and 24 are amended in order to exclude from said claims words or expressions that could make the claim indefinite.

Claims 6, 15, 22 and 30 are amended to clarify their language.

Claims 11, 16 and 24 are amended in order to clarify the scope of the claims. The amended claims now recite that the sevoflurane or a fluoroether compound is combined/mixed with a stabilizer agent. Support for these amendments can be found on page 12 lines 1-17 and 25-29 of the specification as filed.

Claims 7, 18, 26 and 29 are canceled. The subject matter of said claims has been transferred to amended claims 6, 17, 25 and 28, respectively, in order to better define the scope of the claims.

No new matter has been added.

Claims rejection under 35 USC §112

The Examiner rejects claims 1-7 and 11-31 as being indefinite in function of the terms "and the like" and "like". The examined claims do not contain the term "and the like" so, the rejection applies only to the term "like". Claims 1, 2, 11, 16 and 24 were amended in order to exclude the term "like", thus eliminating this rejection.

The Examiner rejects claims 13-31 as being incomplete for omitting essential steps of the method. According to the Examiner, the step of "using at least one stabilizer agent" does not constitute a concrete method step. Applicants respectfully submit that the Examiner's intention was to mention claims 11-31 instead of claims 13-31. Claims 11, 16 and 24 recite the above mentioned expression, and have been amended appropriately to overcome the rejection.

Claims rejection under 35 USC §102

The Examiner rejects claims 1, 16 and 19-21 as being anticipated by Yang et al. (Gaoxiong Yi Xue Ke Xue Zu Zhi, 1990, 6(3), p.127-30 (abstract)). The Examiner states that Yang discloses compositions that are the same as those claimed. Applicants respectfully disagree.

"A rejection for anticipation under section 102 requires that each and every limitation of the claimed invention be disclosed in a single prior art reference." See, *e.g.*, *In re Paulsen*, 31 USPQ2d 1671 (Fed. Cir. 1994), and many other cases.

The abstract of the Yang reference discloses that:

> *This report describes an inhalation anesthetic technique employed in rats. Polyethylene-glycol 400 (PEG 400) was first designed to combine with halothane to produce a slow-releasing system of vaporized halothane. This design provided adequate anesthetic levels for treating with atracurium, a new neuromuscular blocking agent. Furthermore, isoflurane was also used in this study to examine this inhalation system for treating with atracurium. The efficient concentrations of inhalated anesthetics for adequate anesthesia when combining with PEG were 0.15% and 0.1% for halothane and isoflurane, respectively. This safe efficient state of anesthesia was maintained throughout the experimental course for treating atracurium, and might be used in clinical trials.*

As can be seen from the abstract, the intended use of PEG 400 in combination with halothane or isoflurane is to produce a slow-releasing system of vaporized inhalation anesthetic. There is no mention about the concentration of PEG 400 that is employed in combination with halothane or isoflurane. Only the anesthetic concentration of halothane and isoflurane is mentioned. The abstract states that the values 0.15% and 0.1% refer to the concentration of halothane and

isoflurane, respectively, and not to the concentration of PEG-400 as misunderstood by the Examiner ("*The efficient concentrations of inhalated anesthetics ... were 0.15% and 0.1% for halothane and isoflurane, respectively.*") The correct interpretation can be confirmed by reference to the "material and methods" section of the Yang reference (complete document attached) disclosing that 50 ml of halothane was combined with 150 ml of distilled water, PEG 400 or halothane, and were vaporized at 25°C via a vaporizing system. The same preparation method applies to isoflurane. The amount of PEG 400 that was combined with halothane (or isoflurane) was the amount needed for the Yang study purpose; that is to reduce the volatility of halothane (or isoflurane).

On the other hand, in the present invention the fluoroether compound is stabilized against degradation. This purpose requires only very little of the polyalcohol, as now recited in the claims.

Thus, the present invention and the Yang compositions are not the same, and the difference between the claimed invention and the prior art is significant and observable because the claimed composition does not produce a slow-releasing system of vaporized anesthetic. Hence, any and all rejections based on Yang reference are inappropriate and should be withdrawn.

Claim rejections under 35 USC §103

(a). Yang et al (Gaoxiong Yi Xue Ke Xue Zu Zhi, 1990, 6(3), p.127-30 (abstract)) in view of Bieniarz et al. (US5,990,176)

The Examiner rejects claims 1,2, 4, 5, 11, 13, 14, 16, 19-21, 23, 24, 27-29 and 31 under 35 USC § 103(a) as being unpatentable over Yang et al. (Gaoxiong Yi Xue Ke Xue Zu Zhi, 1990, 6(3), p.127-30 (abstract)) in view of Bieniarz *et al.* (US5,990,176).

Applicants respectfully disagree and assert that the cited references fail to establish *prima facie* obviousness of the claimed invention. In order to determine obviousness as a legal matter, four factual inquiries must be made concerning: 1) the scope and content of the prior art; 2) the

level of ordinary skill in the art; 3) the differences between the claimed invention and the prior art; and 4) secondary considerations of nonobviousness, which in case law is often said to include commercial success, long-felt but unresolved need, failure of others, copying, and unexpected results. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). The first three factors relate to establishing *prima facie* obviousness, and the fourth (secondary considerations) relates to providing evidence to overcome any case of *prima facie* obviousness that might be deemed established by the references.

Furthermore, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Additionally, there must be a reason why one of ordinary skill in the art would modify the reference or combine reference teachings to obtain the invention. A patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. *KSR Int'l Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007). There must be a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. *Id.*

Still further, there must be a reasonable expectation of success in making the invention. *In re Vaeck.* Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. *KSR Int'l Co. v Teleflex Inc.*

The instant rejection arises from a misunderstanding by the Examiner about the Yang reference. The Examiner states that "*Yang does not specifically recite providing a sustained release formulation of sevoflurane using 0.1% PEG 400. It is for this reason that Bieniarz is joined.*"

As explained above, in the Yang abstract (and in the complete reference attached) the value 0.1% refers to the amount of anesthetic and does not refer to the amount of PEG-400 as incorrectly interpreted by the Examiner. The claimed composition does not provide a slow-releasing anesthetic composition. Therefore, all of the reasons urged by the Examiner to make a

rejection based on obviousness are not tenable, and these rejections should be withdrawn for this reason alone.

Furthermore, Bieniarz does not cure the deficiency of Yang in failing to describe an amount of polyalcohol to be used in the composition. Thus, at least one feature of the invention is not disclosed or suggested by the combined references, and the rejection of claims 1, 2, 4, 5, 11, 13, 14, 16, 17-21, 23, 24, 27-29 and 31 as obvious over these references should be withdrawn.

With regard to claim 36, Applicants respectfully submit that the Examiner's intention was to mention claim 24 instead of claim 36. The Examiner states that it would be obvious to include 20 ppm water in the formulation because Bieniarz teaches that fluoroether compounds are stabilized from degradation products by inclusion of 0.015 to 0.14% water (column 4, lines 52-60).

At first, it is important to mention that water is inherent to the sevoflurane since this active ingredient is hygroscopic and it is produced and/or purified in an aqueous medium.

The present application has demonstrated that specific amounts of polyalcohols effectively work for both anhydrous sevoflurane (one that contains around 20ppm of water - that is, 0.0020% w/w) and wet sevoflurane (one that contains water up to its saturation level in the sevoflurane, that is 0.14%). See the results presented on tables 4-6 of the specification as filed showing that 260 ppm (0.026% w/w) of water as taught by Bieniarz is not adequate for stabilizing sevoflurane while propylene glycol (260ppm) and propylene glycol plus water (260 ppm each) provide a desired stabilization of sevoflurane. These results would not be expected by the skilled artisan who reads Yang with Bieniarz.

This unexpected experimental result provides objective evidence of unobviousness of claim 24 in view of Yang and Bieniarz. Therefore, the rejection should be withdrawn for this additional reason as well.

(b). Bieniarz et al. (US 5,990,176) in view of Brown *et al.* (Environmental Health perspectives, 1977, 21, p. 185-188).

The Examiner rejects claims 1-3, 8, 11, 12, 16-18, 23-26 and 31 under 35 USC § 103(a) as being unpatentable over Bieniarz et al. (US 5,990,176) in view of Brown *et al.* (Environmental Health perspectives, 1977, 21, p. 185-188).

Applicants respectfully disagree; again the combined references fail to establish *prima facie* obviousness of the claimed invention.

Bieniarz discloses anesthetic compositions comprising sevoflurane and a Lewis acid inhibitor in an amount effective to prevent degradation of sevoflurane by a Lewis acid, said Lewis acid inhibitor being selected from the group consisting of water, butylated hydroxytoluene, methylparaben, propylparaben, propofol and thymol.

The Examiner states that Bieniarz does not specifically recite propylene glycol as a stabilizer, and so Brown is joined.

According to the Examiner, Brown discloses that 1,1,1-trifluoro-2-chloroethane, a debrominated derivative of the inhalation anesthetic halothane, is unstable and should be prepared anaerobically and stored in propylene glycol (abstract). The Examiner concludes that propylene glycol can be used to stabilize unstable fluorinated inhalation anesthetics such as 1,1,1-trifluoro-2-chloroethane.

Some passages of the Brown reference should be considered in order to better interpret the teachings of said reference and consequently show that the combination of references is improper:

- The derivative 1,1,1-trifluoro-2-chloroethane is unstable and thus was prepared anaerobically and trapped in propylene glycol solvent (abstract);

- By use of two stopcocks, the effluent 1,1,1-trifluoro-2-chloroethane was directed and dissolved into the propylene glycol. This product was stable in this solvent as long as it was used stored in dry ice (page 186 - Synthesis);

- This compound is extremely reactive, with a tendency to explode on contact with water (page 186 - Hepatotoxicity);

- Therefore, ca. 1 mg of 1,1,1-trifluoro-2-chloroethane in 0.5 mL propylene glycol was directly injected into the portal vein of rats under pentobarbital anesthesia (page 186 - Hepatotoxicity).

There are many differences between the compound 1,1,1-trifluoro-2-chloroethane and the inhalation anesthetics (sevoflurane, desflurane, isoflurane, enflurane and methoxyflurane) used in the composition of the present invention.

First of all it is important to note that 1,1,1-trifluoro-2-chloroethane is not an inhalation anesthetic. It is a possible metabolite of halothane (an inhalation anesthetic) and the Brown study demonstrated that it is capable of destroying the liver morphology. Neither halothane nor its metabolites are among the compounds recited in the claims. This fact would be enough to show that the rationale by the Examiner for the combination of references is improper, but there are others.

The compound 1,1,1-trifluoro-2-chloroethane tends to explode on contact with water while the inhalation anesthetics claimed do not have this problem, on the contrary, they contain water from the synthetic process and due to their hygroscopic characteristic.

Based on the tested composition (1 mg of 1,1,1-trifluoro-2-chloroethane in 0.519g of propylene glycol - equivalent to 0.5 mL propylene glycol), the structural difference between the composition of Brown and of the claimed composition is clear. The Brown composition is not an anesthetic composition for clinical use as is the case of the claimed composition. So, there is no motivation to combine Bieniarz and Brown, nor any expectation of success in obtaining the claimed composition.

With regard to the claimed amount of propylene glycol considered obvious because Bieniarz teaches 0.015 to 0.14% of stabilizer, the Examiner should reconsider the passage of Bieniarz (US 5,990,176 column 4 lines 53-60) which discloses that: *"The Lewis acid inhibitor preferred for use in the composition of the present invention is water. Purified or distilled water or a combination of both can be used. As stated earlier, the effective amount of water that can be added to the composition is believed to be about 0.0150% w/w to about 0.14% w/w, and is preferably about 0.0400% w/w to about 0.0800% w/w. For any other Lewis acid inhibitor, a molar equivalent based upon moles of water should be used."*

Considering the teachings of Bieniarz, the minimum and the preferred water amounts in mols is, respectively, 8.334×10^{-4} mols (equivalent to 0.015% of water) and 22.2×10^{-4} mols (equivalent to 0.040% of water). Table 1 below shows the minimum and the preferred amounts, in **%,** for the other additives listed by Bieniarz, based on the water mols.

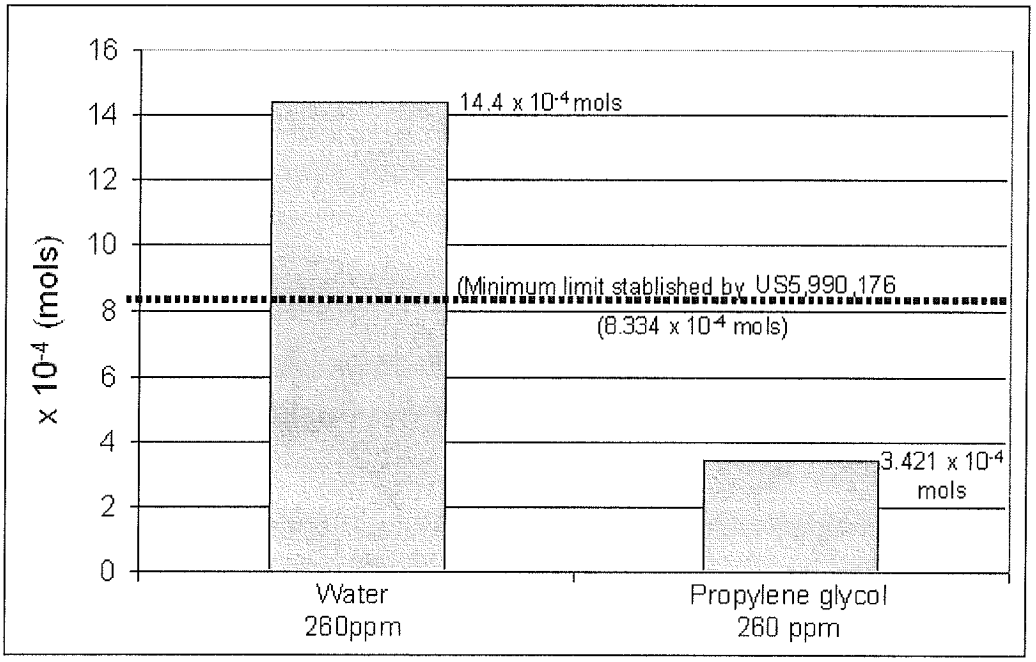
Table 1. Minimum and preferred amount of additives in the Bieniarz compositions.

Compositions		Additive		
Anhydrous active principle (0.005% water)	Additives	Molar mass (g/mol)	Effective minimum amount (%)	Minimum preferred amount (%)
sevoflurane	Water	18	0.015	0.040
sevoflurane	BHT	220.35	0.183	0.489
sevoflurane	Methylparaben	152.15	0.126	0.338
sevoflurane	Propylparaben	180.20	0.150	0.400
sevoflurane	Propofol	178.27	0.149	0.398
sevoflurane	Thymol	150.22	0.125	0.335

According to present application, 260 ppm of water (equivalent to 14.4×10^{-4} mols), proved to be inefficient to stabilize sevoflurane, while 260 ppm of propylene glycol, 3.421×10^{-4} mols, ensures total stability to the product preventing the decomposition thereof (Example 5 from the present specification).

Graph 1, below, allows a better visual evaluation of the difference between 260 ppm (0.026 % w/w) of propylene glycol and water, when represented in mols. The first column (260 ppm of water) reproduces a water amount in mols that cannot stabilize sevoflurane. Meanwhile, the second column from the graph (260 ppm of propylene glycol) reproduces the propylene glycol amount in mols that leads to an effective stabilization of sevoflurane, evidencing that such amount is much lower than the minimum limit for water said to be "effective" by Bieniarz.

Graph 1: Comparison between water and propylene glycol amounts in mols



The above results show that the combined references fail to establish *prima facie* obviousness of the claimed invention. In particular, they show that the combination of Bieniarz with Brown teaches away from the present invention, in that the combined references lead to use of far more of a polyalcohol stabilizer than is recited in the claims. Alternatively, the above results can be considered to show a result that is unexpected by one of ordinary skill in the art who reads Bieniarz with Brown, in that far less of a polyalcohol stabilizer can be used than is suggested by the combination of references.

Hence, the claimed invention is not obvious over the teachings of Bieniarz is taken alone or in view of Brown. Therefore the instant rejection based on said references should be withdrawn.

Applicant respectfully requests immediate allowance of the claims, which define subject matter that meets all statutory patentability requirements.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell, Ph.D., Reg. No. 36,623, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

By _____

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Attachment: Yang et al. *Kaohsiung J. Med Sci* 6:127-130 (1990)